Answer 1:

Bibliographic Information

In vitro and in vivo anti-tumoral activities of imidazo[1,2-a]quinoxaline, imidazo[1,5-a]quinoxaline, and pyrazolo[1,5-a]quinoxaline derivatives. Moarbess, Georges; Deleuze-Masquefa, Carine; Bonnard, Vanessa; Gayraud-Paniagua, Stephanie; Vidal, Jean-Remi; Bressolle, Francoise; Pinguet, Frederic; Bonnet, Pierre-Antoine. Laboratoire de Pharmacochimie et Biomolecules, EA 4215, Faculte de Pharmacie, Universite Montpellier I, Montpellier, Fr. Bioorganic & Medicinal Chemistry (2008), 16(13), 6601-6610. Publisher: Elsevier Ltd., CODEN: BMECEP ISSN: 0968-0896. Journal written in English. AN 2008:731172 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Imidazoquinoxaline and pyrazoloquinoxaline derivs., analogs of imiquimod, were synthesized, and their in vitro cytotoxic and pharmacodynamic activities were evaluated. In vitro cytotoxicity studies were assessed against melanoma (A375, M4Be, RPMI-7591), colon (LS174T), breast (MCF7), and lymphoma (Raji) human cancer cell lines. In vivo studies were carried out in M4Be xenografted athymic mice. EAPB0103, EAPB0201, EAPB0202, and EAPB0203 showed significant in vitro activities against A375 compared to fotemustine and imiquimod used as refs. These compds. were 6-110 and 2-45 times more active than fotemustine and imiquimod, resp. EAPB0203 bearing phenethyl as substituent at position 1 and methylamine at position 4 showed the highest activity. EAPB0203 has also a more potent cytotoxic activity than imiquimod and fotemustine in M4Be and RPMI-7591 and interesting cytotoxic activity in other tumor cell lines tested. In vivo, EAPB0203 treatment schedules caused a significant decrease in tumor size compared to vehicle control and fotemustine treatments.

Answer 2:

Bibliographic Information

Evaluation of the efficiency of chemotherapy in in vivo orthotopic models of human glioma cells with and without 1p19q deletions and in C6 rat orthotopic allografts serving for the evaluation of surgery combined with chemotherapy. Branle, Fabrice; Lefranc, Florence; Camby, Isabelle; Jeuken, Judith; Geurts-Moespot, Anneke; Sprenger, Sandra; Sweep, Fred; Kiss, Robert; Salmon, Isabelle. Department of Oncology, Erasmus University Hospital, Brussels, Belg. Cancer (New York, NY, United States) (2002), 95(3), 641-655. Publisher: John Wiley & Sons, Inc., CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 138:198258 AN 2002:641901 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

BACKGROUND. Malignant gliomas of the central nervous system remain assocd. with dismal prognoses because of their diffuse invasion of the brain parenchyma. Very few exptl. models that mimic clin. reality are available today to test potentially new therapies. The authors set up exptl. in vivo glioma models of anaplastic astrocytomas of human and rat origins and anaplastic oligodendroglioma of human origin. Std. hospital chemotherapies were employed to test the validity of these models. METHODS. Three glioma cells lines obtained from the American Type Culture Collection (i.e., human Hs683 and U373 cells and rat C6 cells) were implanted into nude mouse brains (Hs683 and U373 cells) and rat brains (C6 cells). The astrocytic nature, as opposed to the oligodendrocytic nature, of the Hs683 and U373 models was investigated by using quant. (computer-assisted microscopy) immunohistochem. characterizations of nestin, vimentin, glutathione-S-transferase α (GSTα), GSTμ, GSTπ, and p53 expression. Comparative genomic hybridization (CGH) was employed to investigate 1p19q losses. Chronic administrations of carmustine (BCNU), fotemustin, or temozolomide were assayed in the xenografted U373 and Hs683 models. Both BCNU-related chemotherapy and surgery were assayed in the C6 model. RESULTS. The quant. phenotypic analyses pointed to the oligodendroglial nature of the Hs683 cell line and the astrocytic nature of the U373 cell line. The Hs683 cells exhibited 1p19q losses, whereas the U373 cells did not. BCNU, fotemustin, and temozolomide dramatically increased the time of survival of the Hs683 oligodendroglioma-bearing mice, whereas temozolomide only induced a weak but nevertheless statistically significant increase in the U373 glioma-bearing mice. In the C6 rat glioma model, surgery and BCNU chemotherapy were more efficient than either treatment alone. CONCLUSIONS. The in vivo models of gliomas of the central nervous system developed in the current work best mimicked clin. reality.

They can be used either to identify new therapies against human gliomas or to optimize existing therapies.

Answer 3:

Bibliographic Information

Antitumor effects of fotemustine and busulfan against a human neuroblastoma xenograft. Ikeda, Hitoshi; Tsuchida, Yoshiaki; Wu, Jianguo; Suzuki, Norio; Kuroiwa, Minoru; Choi, Seung Hoon; Morikawa, Akihiro. The Department of Surgery, Gunma Children's Medical Center, Gunma, Japan. Oncology Reports (2000), 7(6), 1265-1268. Publisher: Oncology Reports, CODEN: OCRPEW ISSN: 1021-335X. Journal written in English. CAN 134:275409 AN 2000:765893 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We examd. whether or not fotemustine, a new nitrosourea deriv., and busulfan, an agent already clin. used, are effective against human neuroblastoma, using a human neuroblastoma xenograft model designated TNB9. The max. inhibition rate (MIR) of fotemustine against the TNB9 model was 44.6% with a total dose of fotemustine of 75 mg/kg, indicating that fotemustine is not effective against TNB9. The MIR of busulfan against the same model was 26.7% when a total dose of 135 mg/kg was administered orally to nude mice. Busulfan was also suspended in CM-cellulose, and was administered i.p. The MIRs were 19.4% and 36.4% when busulfan was administered i.p. at a total dose of 40 mg/kg and 60 mg/kg, resp. The total doses of 40 mg/kg and 60 mg/kg did not show any adverse effects on mice, but were found to be ineffective against TNB9, indicating that busulfan might not be an effective chemotherapeutic agent against human neuroblastoma.

Answer 4:

Bibliographic Information

Activity of fotemustine in medulloblastoma and malignant glioma xenografts in relation to O6-alkylguanine-DNA alkyltransferase and alkylpurine-DNA N-glycosylase activity. Vassal, Gilles; Boland, Isabelle; Terrier-Lacombe, Marie-Jose; Watson, Amanda J.; Margison, Geoffrey P.; Venuat, Anne-Marie; Morizet, Jackie; Parker, Fabrice; Lacroix, Catherine; Lellouch-Tubiana, Arielle; Pierre-Kahn, Alain; Gwenaelle Poullain, Marie; Gouyette, Alain. Laboratory of Pharmacotoxicology and Pharmacogenetics (Centre National de la Recherche Scientifique URA 147), Institut Gustave-Roussy, Villejuif, Fr. Clinical Cancer Research (1998), 4(2), 463-468. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 128:239084 AN 1998:130545 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Fotemustine is a chloroethylnitrosourea with antitumor activity in disseminated melanoma and adult primary brain tumors. Because new drugs are required for the treatment of medulloblastoma in children, the authors evaluated the preclin. antitumor activity of fotemustine in four s.c. medulloblastoma xenografts, in comparison with 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU). Both drugs were administered as a single i.p. injection to nude mice bearing advanced-stage tumor. Fotemustine displayed significant antitumor activity in three of four medulloblastoma xenografts; two, IGRM34 and IGRM57, were highly sensitive, with 37 and 100% tumor-free survivors, resp., more than 120 days after treatment at the highest non-toxic dose (50 mg/kg). Fotemustine was also highly active in a malignant glioma xenograft (IGRG88; five of six tumor-free survivors on day 177). Fotemustine proved to be significantly more active than BCNU in IGRM34 and the glioma xenograft IGRG88. The DNA repair protein O6-alkylguanine-DNA alkyltransferase (ATase) was detected in all tumor xenografts, ranging in activity from 6 to 892 fmol/mg protein. The high in vivo sensitivity to fotemustine and BCNU obsd. in three xenografts was clearly assocd. with a low ATase activity (<20 fmol/mg), whereas the two poorly sensitive or refractory medulloblastoma xenografts showed high ATase activity (>500 fmol/mg). Alkylpurine-DNA N-glycosylase activity was detected in all tumor xenografts but at levels ranging only from 513 to 1105 fmol/mg/h; no consistent relation was found between alkylpurine-DNA N-glycosylase activity and the in vivo sensitivity to the two chloroethylnitrosoureas. The improved activity and tolerance of fotemustine in comparison with BCNU in pediatric medulloblastoma xenografts strongly support the clin. development of this agent in children with brain tumors, in which ATase should be examd. as a potential prognostic indicator.

Answer 5:

Bibliographic Information

Effects of paclitaxel, fotemustine, irinotecan, mitomycin C, ifosfamide and bleomycin on a highly malignant xeno-transplanted neuroblastoma. Choi, S. H.; Tsuchida, Y.; Kamii, Y.; Yang, H.W.; Komuro, H.; Makino, S. Department of Pediatric Surgery, University of Tokyo, Tokyo, Japan. Cancer Journal (1996), 9(6), 323-327. Publisher: Association pour le Developpement de la Communication Cancerologique, CODEN: CANJEI ISSN: 0765-7846. Journal written in English. CAN 126:126629 AN 1997:109558 CAPLUS

Abstract

Although the prognosis for patients with neuroblastoma has improved in recent years, new, highly effective, less toxic therapeutic regimens are needed to achieve better outcomes. The purpose of this study was to assess the efficacy of six new and old chemotherapeutic agents on a human neuroblastoma xenograft, designated TNB9, according to the std. Battelle Columbus Labs. protocol. Cytogenetic and phenotypic analyses showed that TNB9 is one of the most malignant strains among human neuroblastoma xenografts. When the estd. TNB9 tumor wt. reached 100 to 200 mg, 49 female nu/nu BALB/c tumor-bearing mice were randomly divided into 7 groups. One of six drugs was administered i.p. in a total of three doses at four-day intervals to the mice in each exptl. group, while the control group received injections of normal saline. The doses of these agents at each injection were equiv. to one-third of the LD50. The results were evaluated on the basis of the max. inhibition rate and also by the degree of tumor regression. Maximum inhibition rates were as follows: mitomycin C, 95.6%; ifosfamide, 91%; irinotecan (CPT-11), 72.5%; bleomycin, 72%; fotemustine, 55.7%; and paclitaxel, 46.4%. Assessment of chemotherapeutic sensitivity in vivo showed that irinotecan, mitomycin C, ifosfamide, and bleomycin were active agents, whereas paclitaxel and fotemustine had minimal or marginal activity in the treatment of neuroblastoma.

Answer 6:

Bibliographic Information

Modulating nitrosourea response in tumors and normal tissue: application to fotemustine. Margison, G. P.; Rafferty, J. A.; Elder, R. H.; Kelly, J.; Watson, A. J.; Willington, M. A.; Lee, S.-M.; Hickson, I.; Fairbairn, L. J. CRC Department of Carcinogenesis, Trinity College, University of Dublin, Peru. Drugs of Today (1996), 32(Suppl. E, Cerebral Tumors and Disseminated Malignant Melanoma: Outlook for a Better Prognosis), 51-59. Publisher: Prous, CODEN: MDACAP ISSN: 0025-7656. Journal written in English. CAN 126:84209 AN 1997:36614 CAPLUS

Abstract

Fotemustine (Muphoran) is a chloroethylnitrosourea (CNU) and, by analogy with other CNUs, its principal mechanism of cell killing is likely to be via the formation of a chloroethylating species that generates C-G interstrand crosslinks in DNA following an initial chloroethylation reaction at the O6-position of guanine residues. CNU-mediated DNA crosslink formation can be prevented by the action of the DNA repair protein, O6-alkylguanine-DNA alkyltransferase (ATase), on the initial O6-chloroethylguanine monoadduct. Several groups have shown that overexpression of ATase in mammalian cells in culture following transfection of pro- or eukaryotic ATase-encoding expression vectors protects against the toxic effects of CNUs, including fotemustine, demonstrating that this is indeed the principal mechanism of resistance to such agents, although other mechanisms, including the action of DNA glycosylases, cannot be discounted. Many of the tumor types that the authors have immunostained with anti-human ATase antibodies express high levels of this protein, but regional variations in immunostaining within a tumor and different levels of immunostaining in different melanoma metastases from the same patient have also been seen. On the other hand, bone marrow, the principal site of dose-limiting toxicity for most nitrosoureas, generally expresses relatively little ATase activity. ATase in tumor cells can be depleted by the administration of O6-alkylguanines that act as substrates for the protein, and this increases the growth inhibitory effect of CNUs and related agents in several human tumor xenografts grown in nude mice. Increasing the ATase levels in murine bone marrow by the ex vivo transduction of retroviruses encoding human ATase into bone marrow cells decreases their sensitivity to the toxic effects of this class of agents. Similar modulations of ATase levels might, therefore, be expected to increase the therapeutic index of fotemustine and other CNUs when used clin.